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Multicomponent Reactions

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Summary

Multicomponent reactions

Studies toward Scaffold and Stereochemical Diversity

Multicomponent reactions (MCRs) are highly flexible, convenient reactions to rapidly generate complex and diverse small molecules. As such they are very suitable to access unexplored regions of chemical space in a Diversity Oriented Synthetic (DOS) approach. They also form the basis for modular reaction sequences, a conceptual new approach to DOS, which consists of a combination of MCRs and other complexity-generating reactions, like cycloadditions, condensations or even additional MCRs. In these sequences a densely functionalized reactive intermediate, like a 1-azadiene, is formed *via* an initial MCR that can react with different additional components yielding a diverse set of complex scaffolds. However, an inherent problem of using MCRs is the lack of stereocontrol over newly formed stereocenters.

The research described in this thesis focuses on two different subjects: (i) the use of MCRs for the generation of scaffold diversity *via* modular reaction sequences using 1-azadienes and (ii) possible approaches toward stereoselective MCRs.

1-Azadienes in cycloaddition and multicomponent reactions towards N-heterocycles

1-Azadienes are extremely versatile building blocks for the efficient synthesis of nitrogen heterocycles, which can be found in many biologically active small molecules. The reason for this versatility is the various possible reactivities of 1-azadienes (see Figure 1).

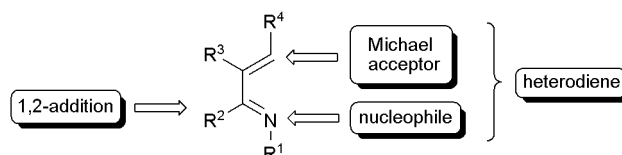
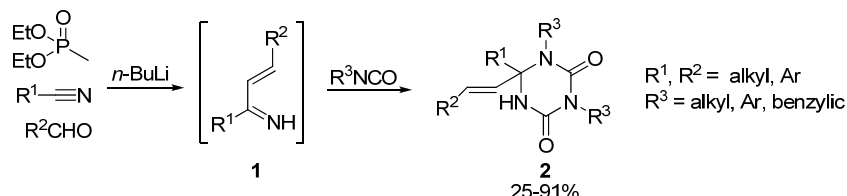


Figure 1: Different reactivities of 1-azadienes.

1-Azadienes can react as nucleophiles, electrophiles and as dienophiles, dipolarophiles or carbenophiles. In chapter 2, various applications of 1-azadienes in cycloaddition, electrocyclization, and multicomponent reactions for the efficient construction of a broad range of N-heterocycles are described. The 1-azadienes are reactive intermediates in these syntheses and are either generated *in situ* or isolated and then used for further reactions. Also the use of 1-azadienes to generate complexity and diversity in several scaffolds is highlighted. They prove excellent platforms to address skeletal diversity in DOS. Especially in combination with MCR-based strategies, 1-azadienes represent a challenging array of functionalities that can be employed to explore chemical space efficiently and identify small molecular probes for biology.

A multicomponent synthesis of triazinane diones

One type of N-heterocycle that can be formed from the 1-azadiene *via* a MCR is the triazinane dione (**2**, Scheme 1). Reaction between diethyl methylphosphonate, a nitrile and an aldehyde yields 1-azadiene **1**, which is then reacted with 2 equivalents of isocyanate yielding the triazinane dione **2** (Scheme 1).



Scheme 1: Multicomponent synthesis of triazinane diones.

First, the reaction conditions were optimized and after that a study of the scope of compatible inputs was conducted. This yielded a small library of 17 different triazinane diones in reasonable to good yields (25-91%). (Hetero)aromatic and aliphatic substituents on the nitrile and aldehyde can be used and benzylic and aromatic substituents on the isocyanate are tolerated. Chiral inputs can also be used in the reaction resulting in a maximum *de* of 67% of the triazinanedione **2**.

Generation of molecular diversity using a complexity-generating MCR-platform toward triazinane diones

Next, research was conducted to investigate if the triazinane dione scaffold could be used as a platform for the generation of diverse sets of relatively complex small molecules. For this, the triazinane dione was first alkylated to afford a scaffold with an appropriate synthetic handle to allow follow-up chemistry.

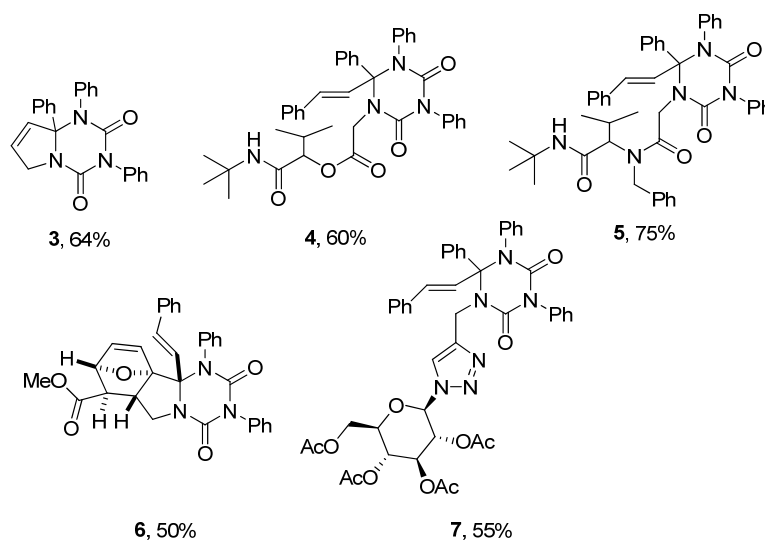
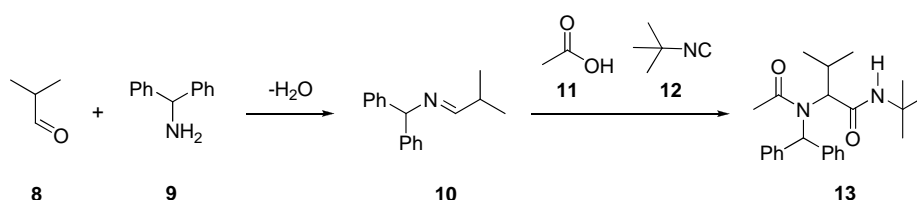


Figure 2: Different scaffolds obtained.

Then additional complexity-generating reactions were performed, like the ring-closing metathesis, cycloaddition reactions (Huisgen or Diels-Alder) and isonitrile-based MCRs (Passerini or Ugi). All five different products (**3-7**, Figure 2) could be obtained in good yields (50-75%) in very short reaction sequences (maximum of four). This nicely demonstrates that the triazinane dione core **2** is indeed a versatile platform to generate efficiently both diversity and complexity.

Mechanistic studies toward a stereoselective Ugi reaction

The research described in chapter 5 deals with studies toward a stereoselective Ugi-reaction (U-4CR) using chiral catalysts. The design of a suitable catalyst for an enantioselective U-4CR depends on our understanding of the exact reaction mechanism. Therefore, a thorough study of critical reaction parameters was required. A model reaction (Scheme 2) was chosen to study the influence of solvent, temperature and acid concentration on the performance of the U-4CR. This should lead to the selection of optimal conditions for a screening of potential asymmetric catalysts.



Scheme 2: Standard Ugi-reaction.

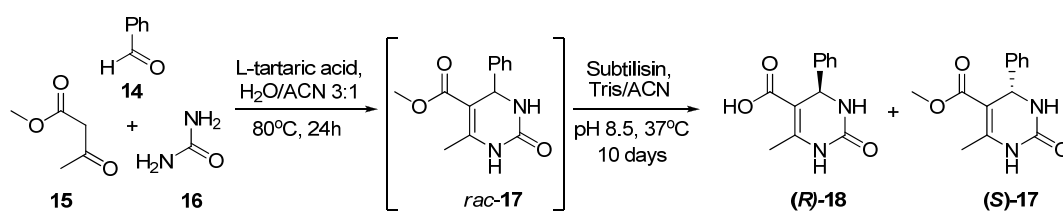
The study revealed that in methanol the U-4CR proceeds too fast to study any catalysis. However, a combination of dichloromethane or toluene and a temperature of -5 °C seemed reasonable conditions to study asymmetric catalysis. It was also found that the reaction can be accelerated using methanol at low temperatures, and that the reaction does not reach completion using a catalytic amount of acetic acid in the presence of 1 equivalent of acetate. Next, a suitable Lewis acid for activation of the imine proved scandium triflate, which, in combination with 1 equivalent of sodium acetate afforded the Ugi-product in reasonable to good yields. Using a substoichiometric amount (33%) of Sc(OTf)₃ in trifluoroethanol, the reaction can be driven to completion. Initial screening of several chiral ligands in combination with Sc(OTf)₃ yielded **13** with a maximum of 10% *ee* in a reasonable yield (45-60%).

Combining biocatalysis with multicomponent reactions

Another approach to address the problem of stereoselectivity in MCRs would be the combination of them with biocatalysis in a one-pot procedure. As biocatalysis is normally performed in aqueous media, also MCRs are needed that can be performed in aqueous media. Recent studies have demonstrated that many of the classical MCRs (Biginelli, Ugi, Passerini, Strecker and Mannich) can be performed in aqueous media and are thus in principle compatible with biocatalysis. We envisioned a MCR/biotransformation sequence (Scheme 3)

combining an aqueous Biginelli reaction with a specific hydrolase that hydrolyzes the ester functionality in the Biginelli product **17** (Scheme 3). In the kinetic resolution, one of the enantiomers of the racemic Biginelli product **17** is converted to the corresponding carboxylic acid while the other enantiomer remains unaffected.

First, the individual steps of the Biginelli-hydrolase sequence were established. The aqueous Biginelli reaction is performed best in a 3:1 water/acetonitrile mixture with L-tartaric acid as the acid catalyst and overnight stirring at 80°C, resulting in an isolated yield of 85%. The biotransformation is performed best using the hydrolase subtilisin from *Bacillus lentus* (Genencor Purafect 4000L).



Scheme 3: MCR/biotransformation sequence in one pot.

Direct connection of this Biginelli reaction and biotransformation (resulting in a one-pot sequence) proved to be possible in good conversions and *ee*'s for both the acid and the ester.

In conclusion, major challenges still remain in solving stereoselectivity issues in MCRs. On the other hand, however, this research has demonstrated that MCRs provide an ever-expanding toolbox for the generation of scaffold diversity *via* modular reaction sequences.